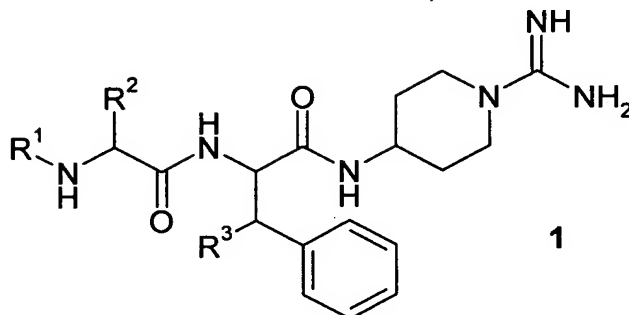


CLAIMS

- 1 A compound according to general formula 1, or a pharmaceutically acceptable salt thereof,

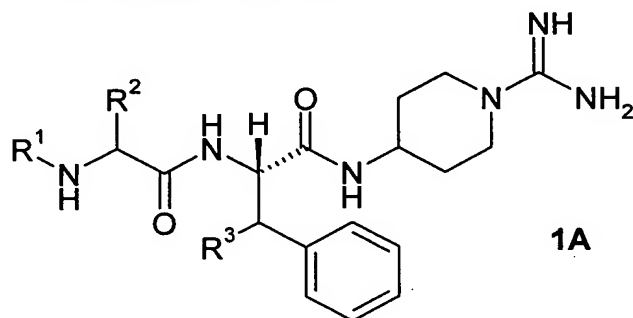


wherein

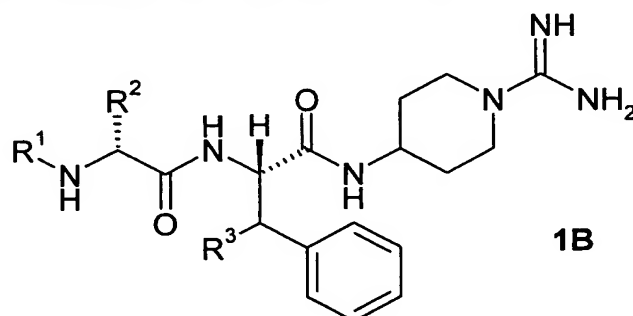
R^1 is selected from H, lower alkyl, R^4 -CO, R^4 -O₂CCH₂, R^5 -OCO and R^5 -SO₂;
 R^2 is selected from lower alkyl, cycloalkyl optionally substituted with an alkyl or alkyloxy group, (C₅-C₁₂)cycloalkylalkyl optionally substituted with an alkyl or alkyloxy group, aralkyl optionally substituted with up to three groups chosen from F, Cl, Br, I, OH, lower alkyl, O-(lower alkyl), O-benzyl, NH₂, NO₂, NH-acyl, CN and CF₃, and aralkyloxymethyl optionally substituted with up to three groups chosen from F, Cl, Br, OH, lower alkyl and O-(lower alkyl); or
 R^1 and R^2 together are an *o*-xylylene group optionally substituted on the aromatic ring with a group selected from F, Cl, Br, OH, lower alkyl and O-(lower alkyl);
 R^3 is selected from H, OH and O-lower alkyl;
 R^4 is selected from H, lower alkyl and phenyl; and
 R^5 is selected from lower alkyl, phenyl and benzyl.

- 2 A compound according to Claim 1 wherein R^1 is selected from H, lower alkyl, and R^4 -O₂CCH₂.
- 3 A compound according to either of Claims 1 and 2 wherein R^2 is selected from (C₆-C₁₀)cycloalkylmethyl, benzyl optionally substituted with up to three groups chosen from F, Cl, Br, OH, lower alkyl and O-(lower alkyl), phenethyl optionally substituted with up to three groups chosen from F, Cl, Br, OH, lower alkyl and O-(lower alkyl) and benzyloxymethyl optionally substituted with up to three groups chosen from F, Cl, Br, OH, lower alkyl and O-(lower alkyl).

- 4 A compound according to any of Claims 1 to 3 wherein R² is selected from cyclohexylmethyl, decahydronaphth-2-ylmethyl, benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-hydroxybenzyl, 4-(lower alkyl)oxybenzyl, α-hydroxybenzyl, α-methoxybenzyl, phenethyl and benzyloxymethyl.
- 5 A compound according to any of Claims 1 to 4 wherein the absolute stereochemistry is as depicted in general formula 1A.



- 6 A compound according to any of Claims 1 to 5 wherein the absolute stereochemistry is as depicted in general formula 1B.



- 7 A compound according to any of Claims 1 to 6 selected from
- (2'*S*, 2''*R*)-4-(2'-(2''-amino-3''-(4'''-ethoxyphenyl)propanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidino;
- (2'*S*, 2''*R*)-4-(2'-(2''-carboxymethylamino-3''-(4'''-ethoxyphenyl)propanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidino;

(2'S,2''R)-4-(2'-(3''-(4'''-ethoxyphenyl)-2''-(methyloxycarbonylmethylamino)-propanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-amino-3''-cyclohexylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-carboxymethylamino-3''-cyclohexylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(3''-cyclohexyl-2''-(methyloxycarbonylmethylamino)propanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-amino-3''-phenylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-carboxymethylamino-3''-phenylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-(methyloxycarbonylmethylamino)-3''-phenylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-amino-3''-decahydronaphth-2'''-ylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(2''-carboxymethylamino-3''-decahydronaphth-2'''-ylpropanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R)-4-(2'-(3''-decahydronaphth-2'''-yl-2''-(methyloxycarbonylmethylamino)propanoylamino)-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R,3'R)-4-(2'-(2''-amino-3''-cyclohexylpropanoylamino)-3'-hydroxy-3'-phenylpropanoylamino)piperidine-1-carboxamidine;

(2'S,2''R,3'R)-4-(2'-(2''-carboxymethylamino-3''-cyclohexylpropanoylamino)-3'-

hydroxy-3'-phenylpropanoylamino)piperidine-1-carboxamide;

(2'*S*,2''*R*,3'*R*)-4-(2'-(3''-cyclohexyl-2''-(methyloxycarbonylmethylamino)-propanoylamino)-3'-hydroxy-3'-phenylpropanoylamino)piperidine-1-carboxamide;

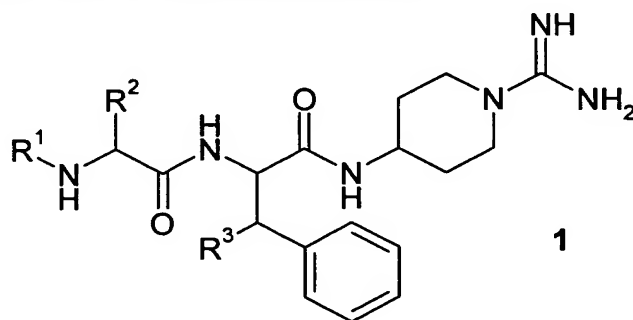
(2'*S*,2''*R*,3'*R*)-4-(2'-(2''-amino-3''-(4'''-ethoxyphenyl)propanoylamino)-3'-methoxy-3'-phenylpropanoylamino)piperidine-1-carboxamide;

(2'*S*,2''*R*,3'*R*)-4-(2'-(2''-carboxymethylamino-3''-(4'''-ethoxyphenyl)propanoylamino)-3'-methoxy-3'-phenylpropanoylamino)piperidine-1-carboxamide; and

(2'*S*,2''*R*,3'*R*)-4-(2'-(3''-(4'''-ethoxyphenyl)-2''-(methyloxycarbonylmethylamino)-propanoylamino)-3'-methoxy-3'-phenylpropanoylamino)piperidine-1-carboxamide

or a pharmaceutically acceptable salt thereof.

- 8 A pharmaceutical composition comprising a compound according to any of Claims 1 to 7 or a pharmaceutically acceptable salt thereof.
- 9 A method of treatment of a disease condition for which over activity of plasma kallikrein is a causative factor comprising administration to a patient in need thereof of a pharmaceutically active amount of compound of general formula 1, or a pharmaceutically acceptable salt thereof,



wherein

R¹ is selected from H, lower alkyl, R⁴-CO, R⁴-O₂CCH₂, R⁵-OCO and R⁵-SO₂;

R² is selected from lower alkyl, cycloalkyl optionally substituted with an alkyl or

alkyloxy group, (C₅-C₁₂)cycloalkylalkyl optionally substituted with an alkyl or alkyloxy group, aralkyl optionally substituted with up to three groups chosen from F, Cl, Br, I, OH, lower alkyl, O-(lower alkyl), O-benzyl, NH₂, NO₂, NH-acyl, CN and CF₃, and aralkyloxymethyl optionally substituted with up to three groups chosen from F, Cl, Br, OH, lower alkyl and O-(lower alkyl); or R¹ and R² together are an o-xylylene group optionally substituted on the aromatic ring with a group selected from F, Cl, Br, OH, lower alkyl and O-(lower alkyl);

R³ is selected from H, OH and O-lower alkyl;

R⁴ is selected from H, lower alkyl and phenyl; and

R⁵ is selected from lower alkyl, phenyl and benzyl.

- 10 A method according to claim 9 for the treatment of inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post-operative surgery.
- 11 The use, in the manufacture of a medicament for treatment of disease in a human or animal, of a compound according to any of claims 1 to 7.
- 12 A pharmaceutical composition according to claim 8 for the treatment of a disease condition for which over activity of plasma kallikrein is a causative factor.